Cleavage and reactions of some NH-BOC protected 1-aminopyrroles: a new one-pot route to pyrrolo[1,2-b][1,2,4]triazines together with spectroscopic and X-ray studies

Orazio A. Attanasi,[a] Lucia De Crescentini,[a] Elisabetta Foresti,[b] Giuseppe Gatti,[c] Raffaello Giorgi,[d] Francesca R. Perrulli[a] and Stefania Santeusanio *,[a]

[a] Istituto di Chimica Organica della Facoltà di Scienze, Università di Urbino, Piazza della Repubblica 13, 61029 Urbino, Italy

[b] Dipartimento di Chimica 'G. Ciamician', Università di Bologna, Via Selmi 2, 40126 Bologna, Italy

[c] Istituto di Scienze Chimiche della Facoltà di Scienze, Università di Urbino, Piazza Rinascimento 6, 61029 Urbino, Italy

[d] Laboratori Guidotti S.p.A., Via Livornese 897, 56122 S. Piero a Grado (Pisa), Italy

1-NH-BOC protected 1,2-diaminopyrroles have been converted by one-pot cleavage of the protecting group and subsequent reaction of the compounds obtained with 1,2-dicarbonyl compounds into highly substituted pyrrolo[1,2-b][1,2,4]triazines. Structural assignments to the regioisomers arising from the reaction with phenylglyoxal have been made on the basis of NMR spectral evidence. An X-ray crystal structure analysis of 6-ethoxycarbonyl-7-methyl-3-phenyl-5-piperidin-1-ylcarbonylpyrrolo[1,2-b]-[1,2,4]triazine has been carried out in order to confirm unambiguously the structure assignment.

The remarkable utility of 1,2-diazabuta-1,3-dienes (currently named conjugated azoalkenes) as important tools in organic chemistry has been well documented.[1–5] In particular, the usefulness of these compounds in the direct synthesis of poly-functionalized pyrrole, pyrazole and thiazole systems has been highlighted.[4,5] The presence of different functional groups in many positions of these heterocycles has been especially emphasised since such compounds have, in turn, potential for further interesting structural modifications, making them suitable as intermediates for more complex compounds. Moreover, as we have already pointed out, some of these substituents may also be considered as protecting groups of functions profitable from the preparative point of view after proper deprotection.[4,6]

With this background, we decided to investigate the hydrolytic cleavage of some 1,2-diaminopyrroles 1 having a 1-NH-BOC protected amino function[8] followed by reaction of the products obtained with 1,2-dicarbonyl derivatives 2 with the aim of finding a new route to highly substituted molecules such as pyrrolo[1,2-b][1,2,4]triazines 5.[3] Compounds containing the 1,2,4-triazine ring show biological activity and are found in natural materials; a large number of such synthetic compounds are also used as pharmaceuticals, pesticides and dyes.[7]

Results and discussion

In order to further our aim, we tried initially three different routes: a direct method (path B) and two indirect methods (path A and path C), as shown in Scheme 1. We generally observed either lower or at best comparable yields by the indirect methods compared with the direct method. This behaviour can be ascribed to the loss of material in the manipulations for the isolation of the intermediates 3 and 4. Hence, in view of the less complicated work-up procedures we considered it more convenient to investigate in detail the one-flask reactions both for the deprotection and condensation steps.

1-BOC protected 1,2-diaminopyrroles 1a–d were allowed to react with 1,2-dicarbonyl compounds 2a–e in acidic tetrahydrofuran to afford directly pyrrolo[1,2-b][1,2,4]triazine derivatives 5a–x (see Scheme 1 and Table 1).
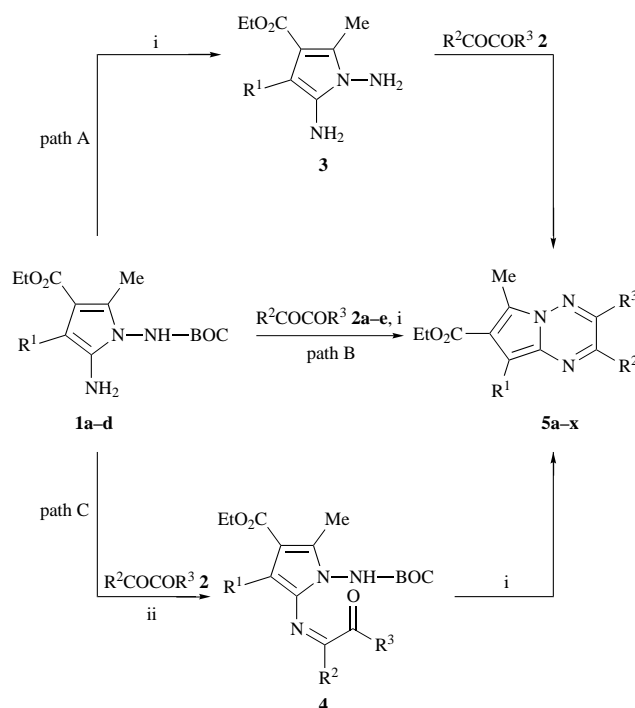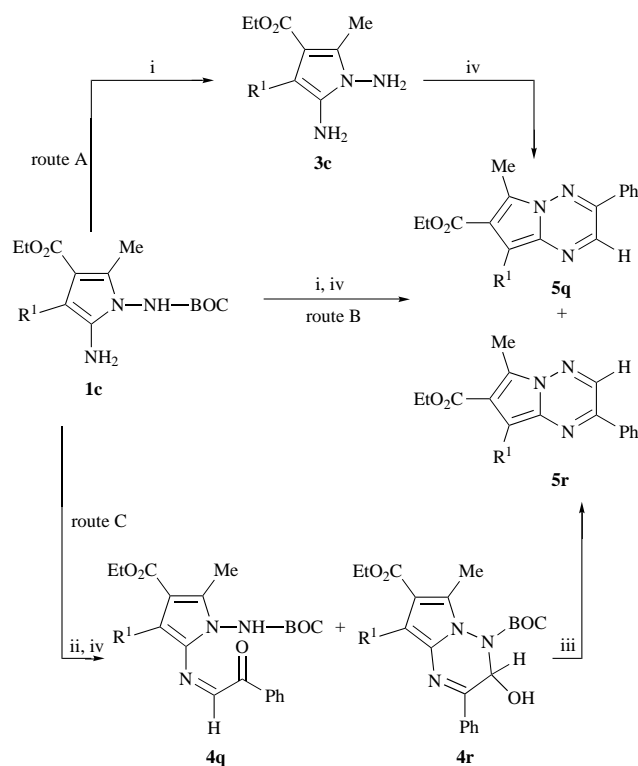

Scheme 1 *Reagents and conditions*: i, 35% Aq. HCl (5.7 equiv.), THF; ii, 35% HCl (cat.), THF

Hydrogen chloride-promoted cleavage of the BOC group and nucleophilic addition to the carbonyl compound gave the fully aromatic fused system by a double condensation process. The reaction of 1-BOC protected 1,2-diaminopyrroles 1a–d with phenylglyoxal monohydrate 2e represented an exception to the general procedure in that the presence of unsymmetric substituents on the dicarbonyl compound together with the aldehydic function in the hydrate form produced two regioisomeric pyrrolo[1,2-b][1,2,4]triazine derivatives: namely 5e and 5f, 5k and 5l, 5q and 5r and 5w and 5x. A detailed study of the reaction between the pyrrole derivative 1c and phenylglyoxal

Table 1

1	R¹	Starting materials 2	R²	R³	Products 4 and 5	R²	R³	Yield (%) Path A	Yield (%) Path B	Yield (%) Path C
1a	$4\text{-}NO_2C_6H_4$	2a	H	H	5a	H	H		32	
		2b	Me	Me	5b	Me	Me		72	
		2c	-(CH₂)₄-		5c	-(CH₂)₄-			31	
		2d	Ph	Ph	5d	Ph	Ph		60	
		2e	Ph	H	5e	H	Ph		11	
					5f	Ph	H		75	
1b	CN	2a	H	H	5g	H	H		79	
		2b	Me	Me	5h	Me	Me		77	
		2c	-(CH₂)₄-		5i	-(CH₂)₄-			43	
		2d	Ph	Ph	5j	Ph	Ph		86	
		2e	Ph	H	5k	H	Ph		44	
					5l	Ph	H		22	
1c	CO-Piperidine	2a	H	H	5m	H	H		63	
		2b	Me	Me	5n	Me	Me		79	
		2c	-(CH₂)₄-		5o	-(CH₂)₄-			56	
		2d	Ph	Ph	5p	Ph	Ph		88	
		2e	Ph	H	4q	H	Ph			73
					5q	H	Ph	54	38	71
					4r	Ph	H			6
					5r	Ph	H	7	28	69
1d	$PO(OEt)_2$	2a	H	H	5s	H	H		35	
		2b	Me	Me	5t	Me	Me		62	
		2c	-(CH₂)₄-		5u	-(CH₂)₄-			22	
		2d	Ph	Ph	5v	Ph	Ph		47	
		2e	Ph	H	5w	H	Ph		43	
					5x	Ph	H		8	

Scheme 2 *Reagents and conditions*: i, 35% HCl (5.7 equiv.), THF; ii, 35% HCl (cat.), THF; iii, 170 °C; iv, PhCOCOH·H₂O

Table 2 ¹H NMR chemical shifts of the 7-methyl group

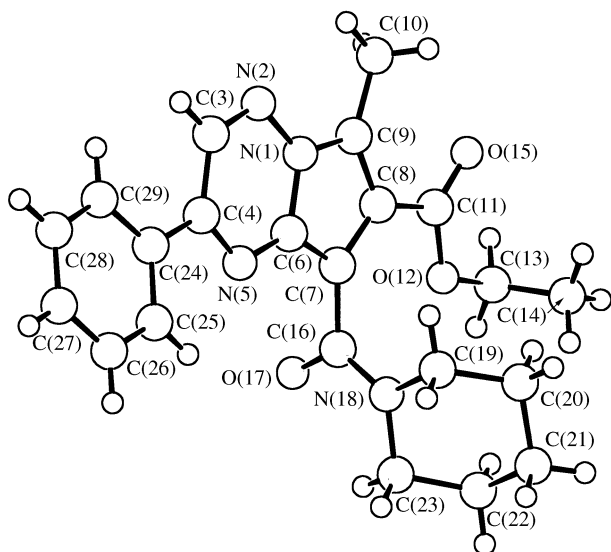| 5-Substituent	5	δ (ppm) 2-Phenyl-regioisomer	5	δ (ppm) 3-Phenyl-regioisomer	Difference
4-Nitrophenyl	5e	2.933	5f	2.886	0.047
Cyano	5k	2.926	5l	2.879	0.047
Piperidin-1-ylcarbonyl	5q	2.879	5r	2.829	0.050
Diethylphosphono	5w	2.810	5x	2.764	0.046

and **5r** (7%) (see Table 1). In an acidic medium, the direct route B, gave the two regioisomers **5q** (38%) and **5r** (28%) in almost comparable yields.

By using a catalytic amount of hydrogen chloride (path C) it was possible to isolate the intermediates **4** and determine that the yield of **4q** (73%) exceeded the yield of **4r** (6%) (see Table 1). In this case, the first step is a nucleophilic attack by the aromatic amino group on the aldehydic function. The structures of the imino derivatives **4q** and **4r**, were assigned through ¹H and ¹³C NMR spectroscopy. When heated in an oil-bath at 170 °C, **4q** and **4r** gave rise to the corresponding pyrrolo[1,2-*b*][1,2,4]triazine derivatives **5q** (71%) and **5r** (69%) (yields refer to the precursors **4q** and **4r**, respectively).

Structure determination

Assignment of structure to the 2-/3-phenyl regioisomers was tentatively made on the basis of the ¹H chemical shifts of the 7-methyl group, which are summarised in Table 2 for the various 5-substituents. The consistent observation of a 0.05 ppm deshielding of this group in one isomer, relative to the other isomer, suggests a proximity of the co-planar phenyl group. In fact, the magnetic anisotropy cone of the phenyl group in position 2 is more deshielding than that in position 3.

In order to check this assignment, the two isomers **5q** and **5r** were synthesised by heating at 170 °C the corresponding precursors **4q** and **4r**, respectively, that had been characterised structurally by spectroscopic evidence. The ¹³C NMR spectrum of compound **4q** showed a signal at δ 190.04, typical for ketonic carbonyl and a signal with DEPT multiplicity of two at δ 150.65 which was assigned to the N=CH fragment;

monohydrate **2e** has also been examined from the mechanistic standpoint (see Scheme 2).

The indirect route A, proceeding by preliminary acidic cleavage of the BOC group, yielded 1,2-diaminopyrrole **3c** which on reaction with the dicarbonyl compound **2e** gave both **5q** and **5r** although the latter was in a low yield. The first step suggests nucleophilic attack by the more basic *N*-amino group at position 1 on the ketonic function followed by attack of the amino group at position 2 of the pyrrole ring on the aldehyde function. In this way, the intermediates rapidly undergo a double condensation process, leading to the aromatic fused systems **5q** (54%)

Fig. 1 The X-ray molecular structure of **5r** with the atom numbering system used in the crystallographic analysis

the ^{1}H NMR spectrum showed the NH signal at δ 10.51 as expected for a 1-BOC protected function. Moreover, the IR spectrum showed absorption at 3168 cm^{-1}. In contrast, compound **4r** showed in its ^{13}C NMR spectrum a DEPT doublet at δ 73.70 and in its ^{1}H NMR spectrum an AB pattern which are attributed to the CHOH group; its IR spectrum showed a broad OH absorption at 3246 cm^{-1}. Moreover, the signal at δ 152.66 (DEPT singlet) was in agreement with the presence of the N=CPh fragment.

A similar procedure was used for the compounds **5e** and **5f**, **5k** and **5l**, **5w** and **5x** with various 5-substituents (see Table 1 and Table 2). For further elucidation of the reaction pathway C, **4f**, **4k** and **4x** were synthesised and their ^{1}H and ^{13}C spectra recorded as for **4q** and **4r**. By heating at 170 °C they gave the corresponding pyrrolo[1,2-*b*][1,2,4]triazine derivatives **5f**, **5k** and **5x**, respectively. As a final check, the structure of **5r** was studied by X-ray diffraction.

The X-ray crystal determination of 6-ethoxycarbonyl-7-methyl-3-phenyl-5-piperidin-1-ylcarbonylpyrrolo[1,2-*b*][1,2,4]-triazine **5r** was in agreement with the conclusions drawn from the ^{1}H NMR evidence. The X-ray molecular structure of **5r** with the atom numbering system used in crystallographic analysis is shown in Fig. 1.

The molecular drawing clearly reveals the five- and six-membered fused rings to be a planar system; the maximum deviation from the plane passing through the nine atoms N(1)−N(2)−C(3)−C(4)−N(5)−C(6)−C(7)−C(8)−C(9) being at C(7) [0.04 Å]. Moreover, the phenyl ring is nearly co-planar with the triazine ring. The torsion angles C(3)−C(4)−C(24)−C(29) and N(5)−C(4)−C(24)−C(25) are 12°.

Experimental

Commercially available solvents were used without further purification except for THF, which was distilled from sodium hydroxide. Glyoxal (40 wt% solution in water) **2a**, butane-2,3-dione **2b**, cyclohexane-1,2-dione **2c**, benzil **2d** and phenylglyoxal hydrate **2e** are commercial materials (Aldrich or Janssen Chimica) and were used without further purification. 2-Amino-1-*tert*-butoxycarbonylamino-3-cyano-4-ethoxycarbonyl-5-methylpyrrole **1b** and 2-amino-1-*tert*-butoxycarbonylamino-4-ethoxycarbonyl-5-methyl-3-piperidin-1-ylcarbonylpyrrole **1c** were prepared as previously reported.[8] New 2-amino-1-*tert*-butoxycarbonylamino-4-ethoxycarbonyl-5-methyl-3-(4-nitrophenyl)pyrrole **1a** and 2-amino-1-*tert*-butoxycarbonylamino-4-ethoxycarbonyl-3-diethylphosphono-5-methylpyrrole **1d** were

synthesised as reported below. Mps were determined in open capillary tubes with a Gallenkamp apparatus and are uncorrected. All yields refer to pure isolated products. All IR spectra were obtained for Nujol mulls and were recorded using a Perkin-Elmer 298 spectrophotometer. Mass spectra were performed with a Hewlett Packard 5995C spectrometer. All ^{1}H and ^{13}C NMR spectra were measured using a Bruker AC-200 (200 MHz) Fourier transform spectrometer equipped with cryomagnet, in CDCl$_3$ solution unless otherwise stated. All the spectra were measured at 298 K. Chemical shifts (δ_H) are reported in ppm downfield from internal Me$_4$Si and J values are given in Hz. The abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and D$_2$O-exch. = D$_2$O exchange. Chemical shifts (δ_C) are reported relative to internal deuteriochloroform or [^{2}H$_6$]dimethyl sulfoxide as internal standard in a broad band decoupled mode; the multiplicities were obtained by using 135 and 90° DEPT experiments to aid in assignments (q = methyl, t = methylene, d = methyne, s = quaternary). Macherey-Nagel pre-coated silica gel SIL G-25UV$_{254}$ plates (0.25 mm thick) were employed for analytical thin layer chromatography (TLC) and silica gel Amicon LC 60 Å (35–70 mm) for column chromatography.

Synthesis of 2-amino-1-*tert*-butoxycarbonylamino-4-ethoxy-carbonyl-5-methyl-3-(4-nitrophenyl)pyrrole 1a

A solution of 1-*tert*-butoxycarbonylazoalkene (1 mmol) in ethyl acetate (5 cm^3) was added at 0 °C to a magnetically stirred solution of 4-nitrophenylacetonitrile (1 mmol) in ethyl acetate (5 cm^3), which had been stirred previously at room temperature for 0.2 h with 1 drop of triethylamine. After the azoalkene had disappeared (monitored by TLC, *ca.* 2 h), ethyl acetate was removed from the mixture by evaporation under reduced pressure to give a residue which was treated with diethyl ether to afford the 1,4-adduct intermediate. The adduct (1 mmol) was refluxed in ethanol in the presence of a catalytic amount of sodium hydride until it had disappeared (monitored by TLC, *ca.* 1.5 h). The red solution was then concentrated under reduced pressure and the precipitated pyrrole derivative **1a** was filtered off to provide a yellow powder (60%), mp 175–176 °C (decomp.) (from ethanol); v_{max}(KBr)/cm^{-1} 3350, 3240, 1700, 1660, 1620, 1600, 1510 and 1340; δ_H 1.13 (3H, t, J 7, CO$_2$CH$_2$*Me*), 1.52 (9H, s, CO$_2$Bu^t), 2.42 (3H, s, Me), 3.47 (2H, s, NH$_2$, D$_2$O-exch.), 4.13 (2H, q, J 7, CO$_2$C*H$_2$*Me), 6.97 (1H, s, NH, D$_2$O-exch.), 7.44 (2H, d, J 8.8, 4-NO$_2$Ph) and 8.19 (2H, d, J 8.8, 4-NO$_2$Ph) (Found: C, 56.52; H, 6.02; N, 13.78%; M$^+$, 404.90. C$_{19}$H$_{24}$N$_4$O$_6$ requires C, 56.43; H, 5.98; N, 13.85%; *M*, 404.42).

Synthesis of 2-amino-1-*tert*-butoxycarbonylamino-4-ethoxy-carbonyl-3-diethylphosphono-5-methylpyrrole 1d

To a stirred solution of diethyl cyanomethylphosphonate (1 mmol) in THF (5 cm^3) and a catalytic amount of sodium hydride at 0 °C was added dropwise 1-*tert*-butoxycarbonyl-azoalkene (1 mmol) dissolved in THF (5 cm^3). The mixture was allowed to warm at room temperature with continuance of the stirring until the azoalkene had disappeared (monitored by TLC, *ca.* 12 h); the reaction mixture was then evaporated under reduced pressure. The residue was dissolved in diethyl ether and the solution washed with water, dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column (cyclohexane–ethyl acetate) to give the title compound as a beige oil (48%); v_{max}(KBr)/cm^{-1} 3440, 3330, 3150, 1740, 1705 and 1610; δ_H([^{2}H$_6$]-DMSO) 1.11–1.32 (9H, m, 2 OCH$_2$*Me* and CO$_2$CH$_2$*Me*), 1.46 (9H, s, CO$_2$Bu^t), 2.18 (3H, s, Me), 3.74–3.93 (4H, m, 2 OC*H$_2$*Me), 4.11 (2H, q, J 7, CO$_2$C*H$_2$*Me), 5.91 (2H, s, NH$_2$, D$_2$O-exch.) and 9.99 (1H, s, NH, D$_2$O-exch.) (Found: C, 48.72; H, 7.35; N, 10.12%; M$^+$, 419.6. C$_{17}$H$_{30}$N$_3$O$_7$P requires C, 48.68; H, 7.21; N, 10.02%; *M*, 419.41).

Synthesis of 1,2-diamino-4-ethoxycarbonyl-5-methyl-3-piperidin-1-ylcarbonylpyrrole 3c

To a stirred solution of the pyrrole derivative **1c** (1 mmol) in THF (2 cm^3) was added at 0 °C aqueous hydrochloric acid (35% w/w; 0.5 cm^3, 5.7 equiv.). After the solution had been allowed to warm at room temperature, stirring was continued until no starting material remained (monitored by TLC, *ca.* 72 h). The reaction mixture was then evaporated under reduced pressure to afford a solid which was suspended in 2 M aqueous NaOH to yield the deprotected pyrrole derivative **3c**. This was collected by suction filtration and then washed with water and dried *in vacuo* to afford a beige powder, mp 175–177 °C (from ethanol); v_{max}(KBr)/cm^{-1} 3440, 3320, 3200, 1725, 1670 and 1640; δ_H([²H₆]-DMSO) 1.21 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.42–1.57 (6H, m, Pip), 2.35 (3H, s, Me), 3.37 (4H, br s, Pip), 4.07 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 4.68 (2H, s, NH$_2$, D$_2$O-exch.) and 5.38 (2H, s, NH$_2$, D$_2$O-exch.) (Found: C, 57.3; H, 7.48; N, 19.12%; M$^+$, 294.65. C$_{14}$H$_{22}$N$_4$O$_3$ requires C, 57.13; H, 7.53; N, 19.03%; *M*, 294.35).

Typical procedure for the synthesis of compounds 5a–x

To a magnetically stirred solution of each of the pyrrole derivatives **1a–d** (1 mmol) and the dicarbonyl compounds **2a–e** (1 mmol) in THF (4 cm^3) was added hydrochloric acid (35% w/w; 0.5 cm^3, 5.7 equiv.) at 0 °C; the reaction mixture was then allowed to warm to room temperature for the appropriate reaction time (monitored by TLC *ca.* 22–72 h). Only **5e–f** required an additional time (2 h) under reflux for the completion. After the reagents disappeared, THF was removed from the mixture under reduced pressure and the residue was dissolved in dichloromethane and the solution neutralised with sodium hydrogen carbonate, washed with water, dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The derivatives **5a–x** were obtained pure either by column chromatography on silica gel (cyclohexane–ethyl acetate mixtures) or directly by crystallisation from the appropriate solvent (see below).

6-Ethoxycarbonyl-7-methyl-5-(4-nitrophenyl)pyrrolo[1,2-*b*]-[1,2,4]triazine 5a

Orange powder, mp 176–177 °C (from dichloromethane–methanol); v_{max}(KBr)/cm^{-1} 1710, 1605, 1505 and 1350; δ_H 1.23 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.86 (3H, s, Me), 4.30 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.71 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$), 8.01 (1H, d, *J* 1.5, CH), 8.16 (1H, d, *J* 1.5, CH) and 8.29 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$) (Found: C, 58.9; H, 4.3; N, 17.2%; M$^+$, 326.65. C$_{16}$H$_{14}$N$_4$O$_4$ requires C, 58.8; H, 4.4; N, 17.1%; *M*, 326.31).

6-Ethoxycarbonyl-2,3,7-trimethyl-5-(4-nitrophenyl)pyrrolo-[1,2-*b*][1,2,4]triazine 5b

Orange crystals, mp 198–199 °C [from tetrahydrofuran–diethyl ether–light petroleum (bp 40–60 °C)]; v_{max}(KBr)/cm^{-1} 1700, 1595, 1505 and 1340; δ_H 1.23 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.50 (3H, s, Me), 2.52 (3H, s, Me), 2.79 (3H, s, Me), 4.28 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.71 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$) and 8.25 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$) (Found: C, 61.1; H, 5.1; N, 15.8%; M$^+$, 354.30. C$_{18}$H$_{18}$N$_4$O$_4$ requires C, 61.2; H, 5.1; N, 15.7%; *M*, 354.36).

6-Ethoxycarbonyl-7-methyl-5-(4-nitrophenyl)-1,2,3,4-tetrahydrobenzo[*e*]pyrrolo[1,2-*b*][1,2,4]triazine 5c

Brownish crystals, mp 179–180 °C (from dichloromethane–methanol); v_{max}(KBr)/cm^{-1} 1700, 1590, 1500 and 1330; δ_H 1.24 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.91–1.98 (4H, m, cyclic CH$_2$), 2.79 (3H, s, Me), 2.90–2.97 (4H, m, cyclic CH$_2$), 4.29 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.70 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$) and 8.25 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$) (Found: C, 63.2; H, 5.2; N, 14.8%; M$^+$, 380.00. C$_{20}$H$_{20}$N$_4$O$_4$ requires C, 63.2; H, 5.3; N, 14.7%; *M*, 380.40).

6-Ethoxycarbonyl-7-methyl-5-(4-nitrophenyl)-2,3-diphenylpyrrolo[1,2-*b*][1,2,4]triazine 5d

Red crystals, mp 188–189 °C (from tetrahydrofuran–diethyl ether); v_{max}(KBr)/cm^{-1} 1710, 1590, 1510 and 1330; δ_H 1.28 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.90 (3H, s, Me), 4.34 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.23–7.46 (10H, m, 2 Ar), 7.83 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$) and 8.28 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$) (Found: C, 70.3; H, 4.5; N, 11.7%; M$^+$, 479.05. C$_{28}$H$_{22}$N$_4$O$_4$ requires C, 70.3; H, 4.6; N, 11.7%; *M*, 478.50).

6-Ethoxycarbonyl-7-methyl-5-(4-nitrophenyl)-2-phenylpyrrolo[1,2-*b*][1,2,4]triazine 5e

Orange crystals, mp 215–218 °C [from chloroform–light petroleum (bp 40–60 °C)]; v_{max}(KBr)/cm^{-1} 1680, 1595, 1505 and 1340; δ_H 1.25 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.92 (3H, s, Me), 4.31 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.55–7.60 (3H, m, Ar), 7.75 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$), 8.00–8.05 (2H, m, Ar), 8.30 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$) and 8.49 (1H, s, CH); δ_C 10.72 (q), 14.79 (q), 61.50 (t), 113.34 (s), 116.84 (s), 123.62 (d), 127.58 (d), 129.14 (s), 130.01 (d), 131.60 (d), 132.12 (d), 133.85 (s), 136.68 (d), 140.55 (s), 147.22 (s), 147.51 (s), 153.11 (s) and 165.62 (s) (Found: C, 65.5; H, 4.5; N, 14.3%; M$^+$, 402.90. C$_{22}$H$_{18}$N$_4$O$_4$ requires C, 65.6; H, 4.5; N, 14.1%; *M*, 402.41).

6-Ethoxycarbonyl-7-methyl-5-(4-nitrophenyl)-3-phenylpyrrolo[1,2-*b*][1,2,4]triazine 5f

Red crystals, mp 213–215 °C (from chloroform); v_{max}(KBr)/cm^{-1} 1680, 1595, 1510 and 1345; δ_H 1.27 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.88 (3H, s, Me), 4.33 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.49–7.55 (3H, m, Ar), 7.81 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$), 8.00–8.06 (2H, m, Ar), 8.30 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$) and 8.70 (1H, s, CH); δ_C 10.73 (q), 14.80 (q), 61.53 (t), 112.81 (s), 117.09 (s), 123.53 (d), 127.08 (d), 128.81 (s), 129.94 (d), 131.32 (d), 132.08 (d), 135.43 (s), 137.76 (d), 140.59 (s), 143.83 (s), 147.01 (s), 153.60 (s) and 165.72 (s) (Found: C, 65.8; H, 4.4; N, 13.7%; M$^+$, 402.70. C$_{22}$H$_{18}$N$_4$O$_4$ requires C, 65.6; H, 4.5; N, 13.9%; *M*, 402.41).

5-Cyano-6-ethoxycarbonyl-7-methylpyrrolo[1,2-*b*][1,2,4]triazine 5g

Yellow powder, mp 128–129 °C (from methanol); v_{max}(KBr)/cm^{-1} 2210 and 1720; δ_H 1.47 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.86 (3H, s, Me), 4.47 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 8.29 (1H, d, *J* 1.7, CH) and 8.32 (1H, d, *J* 1.7, CH) (Found: C, 57.56; H, 4.41; N, 24.12%; M$^+$, 230.85. C$_{11}$H$_{10}$N$_4$O$_2$ requires C, 57.39; H, 4.38; N, 24.34%; *M*, 230.23).

5-Cyano-6-ethoxycarbonyl-2,3,7-trimethylpyrrolo[1,2-*b*][1,2,4]triazine 5h

Yellow crystals, mp 139–141 °C (from tetrahydrofuran–diethyl ether); v_{max}(KBr)/cm^{-1} 2210 and 1710; δ_H 1.48 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.58 (3H, s, Me), 2.62 (3H, s, Me), 2.79 (3H, s, Me) and 4.44 (2H, q, *J* 7, CO$_2$C*H*$_2$Me) (Found: C, 60.4; H, 5.3; N, 21.6%; M$^+$, 258.00. C$_{13}$H$_{14}$N$_4$O$_2$ requires C, 60.45; H, 5.5; N, 21.7%; *M*, 258.28).

5-Cyano-6-ethoxycarbonyl-7-methyl-1,2,3,4-tetrahydrobenzo[*e*]pyrrolo[1,2-*b*][1,2,4]triazine 5i

Brownish crystals, mp 156–157 °C (from tetrahydrofuran–diethyl ether); v_{max}(KBr)/cm^{-1} 2210 and 1710; δ_H 1.46 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.95–2.01 (4H, m, cyclic CH$_2$), 2.78 (3H, s, Me), 3.00–3.05 (4H, m, cyclic CH$_2$) and 4.44 (2H, q, *J* 7, CO$_2$C*H*$_2$Me) (Found: C, 63.4; H, 5.6; N, 19.8%; M$^+$, 284.10. C$_{15}$H$_{16}$N$_4$O$_2$ requires C, 63.4; H, 5.7; N, 19.7%; *M*, 284.32).

5-Cyano-6-ethoxycarbonyl-7-methyl-2,3-diphenylpyrrolo[1,2-*b*][1,2,4]triazine 5j

Orange crystals, mp 183–184.5 °C (from tetrahydrofuran); v_{max}(KBr)/cm^{-1} 2210, 1710 and 1595; δ_H 1.48 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.89 (3H, s, Me), 4.47 (2H, q, *J* 7, CO$_2$C*H*$_2$Me) and 7.30–7.49 (10H, m, 2 Ar) (Found: C, 72.2; H, 4.7; N, 14.7%; M$^+$, 382.00. C$_{23}$H$_{18}$N$_4$O$_2$ requires C, 72.2; H, 4.7; N, 14.65%; *M*, 382.42).

5-Cyano-6-ethoxycarbonyl-7-methyl-2-phenylpyrrolo[1,2-*b*]-[1,2,4]triazine 5k

Yellow powder, mp 212–213.5 °C (from tetrahydrofuran); v_{max}(KBr)/cm^{-1} 2210 and 1700; δ_H 1.49 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.92 (3H, s, Me), 4.48 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.54–7.72 (3H, m, Ar), 7.97–8.12 (2H, m, Ar) and 8.76 (1H, s, CH); δ_C 10.36 (q), 14.80 (q), 62.21 (t), 84.80 (s), 114.00 (s), 118.79 (s), 127.77 (d), 130.20 (d), 130.83 (s), 132.19 (d), 132.88 (s), 137.53 (s), 140.10 (d), 148.45 (s) and 163.47 (s) (Found: C, 66.7; H, 4.7; N, 18.3%; M$^+$, 307.00. C$_{17}$H$_{14}$N$_4$O$_2$ requires C, 66.7; H, 4.6; N, 18.3%; *M*, 306.32).

5-Cyano-6-ethoxycarbonyl-7-methyl-3-phenylpyrrolo[1,2-*b*]-[1,2,4]triazine 5l

Orange powder, mp 247–249 °C (from tetrahydrofuran); v_{max}(KBr)/cm^{-1} 2210 and 1700; δ_H 1.49 (3H, t, *J* 7, CO$_2$-CH$_2$*Me*), 2.87 (3H, s, Me), 4.48 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.56–7.59 (3H, m, Ar), 8.17–8.22 (2H, m, Ar) and 8.83 (1H, s, CH); δ_C 10.41 (q), 14.86 (q), 62.19 (t), 84.11 (s), 114.34 (s), 118.73 (s), 127.86 (d), 130.11 (d), 130.43 (s), 132.08 (s), 132.54 (d), 134.36 (s), 138.46 (d), 147.15 (s) and 163.58 (s) (Found: C, 66.6; H, 4.7; N, 18.5%; M$^+$, 307.00. C$_{17}$H$_{14}$N$_4$O$_2$ requires C, 66.7; H, 4.6; N, 18.3%; *M*, 306.32).

6-Ethoxycarbonyl-7-methyl-5-piperidin-1-ylcarbonylpyrrolo-[1,2-*b*][1,2,4]triazine 5m

Yellow powder, mp 121–122 °C (from tetrahydrofuran–diethyl ether); v_{max}(KBr)/cm^{-1} 1710 and 1625; δ_H 1.37 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.48–1.70 (6H, m, Pip), 2.80 (3H, s, Me), 3.24–3.29 (2H, m, Pip), 3.81–3.86 (2H, m, Pip), 4.35 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.97 (1H, d, *J* 1.7, CH) and 8.08 (1H, d, *J* 1.7, CH) (Found: C, 60.85; H, 6.4; N, 17.7%; M$^+$, 316.10. C$_{16}$H$_{20}$N$_4$O$_3$ requires C, 60.75; H, 6.4; N, 17.7%; *M*, 316.36).

6-Ethoxycarbonyl-2,3,7-trimethyl-5-piperidin-1-ylcarbonyl-pyrrolo[1,2-*b*][1,2,4]triazine 5n

Yellow–orange crystals, mp 159–161 °C [from dichloromethane–light petroleum (bp 40–60 °C)]; v_{max}(KBr)/cm^{-1} 1715 and 1640; δ_H 1.37 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.46–1.69 (6H, m, Pip), 2.48 (6H, s, 2 Me), 2.76 (3H, s, Me), 3.24–3.29 (2H, m, Pip), 3.81–3.86 (2H, m, Pip) and 4.34 (2H, q, *J* 7, CO$_2$C*H*$_2$Me) (Found: C, 62.9; H, 7.1; N, 16.2%; M$^+$, 344.75. C$_{18}$H$_{24}$N$_4$O$_3$ requires C, 62.8; H, 7.0; N, 16.3%; *M*, 344.41).

6-Ethoxycarbonyl-7-methyl-5-piperidin-1-ylcarbonyl-1,2,3,4-tetrahydrobenzo[*e*]pyrrolo[1,2-*b*][1,2,4]triazine 5o

Yellow–orange crystals, mp 166–167 °C [dichloromethane–light petroleum (bp 40–60 °C)]; v_{max}(KBr)/cm^{-1} 1700 and 1635; δ_H 1.37 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.46–1.69 (6H, m, Pip), 1.89–1.96 (4H, m, cyclic CH$_2$), 2.75 (3H, s, Me), 2.89–2.93 (4H, m, cyclic CH$_2$), 3.23–3.28 (2H, m, Pip), 3.80–3.85 (2H, m, Pip) and 4.34 (2H, q, *J* 7, CO$_2$C*H*$_2$Me) (Found: C, 64.75; H, 7.1; N, 15.2%; M$^+$, 370.85. C$_{20}$H$_{26}$N$_4$O$_3$ requires C, 64.85; H, 7.1; N, 15.1%; *M*, 370.45).

6-Ethoxycarbonyl-7-methyl-2,3-diphenyl-5-piperidin-1-ylcarb-onylpyrrolo[1,2-*b*][1,2,4]triazine 5p

Yellow powder, mp 205–208 °C (from tetrahydrofuran); v_{max}(KBr)/cm^{-1} 1715 and 1630; δ_H 1.39 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.43–1.67 (6H, m, Pip), 2.86 (3H, s, Me), 3.33–3.38 (2H, m, Pip), 3.81–3.85 (2H, m, Pip), 4.38 (2H, q, *J* 7, CO$_2$C*H*$_2$Me) and 7.25–7.42 (10H, m, 2 Ar) (Found: C, 71.7; H, 6.1; N, 11.8%; M$^+$, 468.40. C$_{28}$H$_{28}$N$_4$O$_3$ requires C, 71.8; H, 6.02; N, 12.0%; *M*, 468.55).

6-Ethoxycarbonyl-7-methyl-2-phenyl-5-piperidin-1-ylcarbonyl-pyrrolo[1,2-*b*][1,2,4]triazine 5q

Yellow–orange crystals, mp 171–173 °C (from tetrahydrofuran); v_{max}(KBr)/cm^{-1} 1700, 1625 and 1600; δ_H 1.39 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.50–1.70 (6H, m, Pip), 2.88 (3H, s, Me), 3.27–3.33 (2H, m, Pip), 3.83–3.87 (2H, m, Pip), 4.37 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.54–7.57 (3H, m, Ar), 7.97–8.02 (2H, m, Ar) and 8.47 (1H, s, CH); δ_C 10.33 (q), 14.99 (q), 25.34 (t), 26.13 (t), 26.93 (t), 43.40 (t), 48.94 (t), 61.33 (t), 110.82 (s), 115.91 (s), 127.49 (d), 128.55 (s), 129.65 (s), 129.88 (d), 131.38 (d), 133.90 (s), 136.32 (d), 147.01 (s), 164.30 (s) and 164.82 (s) (Found: C, 67.2; H, 6.1; N, 14.2%; M$^+$, 392.30. C$_{22}$H$_{24}$N$_4$O$_3$ requires C, 67.3; H, 6.2; N, 14.3%; *M*, 392.46).

6-Ethoxycarbonyl-7-methyl-3-phenyl-5-piperidin-1-ylcarbonyl-pyrrolo[1,2-*b*][1,2,4]triazine 5r

Red–orange crystals, mp 171–172 °C (from tetrahydrofuran); v_{max}(KBr)/cm^{-1} 1705, 1620 and 1595; δ_H 1.39 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.42–1.72 (6H, m, Pip), 2.84 (3H, s, Me), 3.30–3.35 (2H, m, Pip), 3.84–3.88 (2H, m, Pip), 4.37 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.49–7.51 (3H, m, Ar), 8.04–8.07 (2H, m, Ar) and 8.63 (1H, s, CH); δ_C 10.39 (q), 15.00 (q), 25.43 (t), 26.36 (t), 27.08 (t), 43.45 (t), 49.05 (t), 61.32 (t), 110.48 (s), 116.22 (s), 127.08 (d), 128.15 (s), 129.68 (d), 129.85 (s), 131.04 (d), 135.39 (s), 137.36 (d), 143.31 (s), 164.40 (s) and 164.85 (s) (Found: C, 67.3; H, 6.1; N, 14.2%; M$^+$, 392.30. C$_{22}$H$_{24}$N$_4$O$_3$ requires C, 67.3; H, 6.2; N, 14.3%; *M*, 392.46).

6-Ethoxycarbonyl-5-diethylphosphono-7-methylpyrrolo[1,2-*b*]-[1,2,4]triazine 5s

Dark-orange oil; v_{max}(KBr)/cm^{-1} 1720 and 1030; δ_H 1.20–1.48 (9H, m, 2 OCH$_2$*Me* and CO$_2$CH$_2$*Me*), 2.74 (3H, s, Me), 4.16–4.26 (4H, m, 2 OC*H*$_2$Me), 4.44 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 8.25 (1H, d, *J* 1.7, CH) and 8.27 (1H, d, *J* 1.7, CH) (Found: C, 49.4; H, 6.0; N, 12.3%; M$^+$, 341.35. C$_{14}$H$_{20}$N$_3$O$_5$P requires C, 49.3; H, 5.9; N, 12.3%; *M*, 341.30).

6-Ethoxycarbonyl-5-diethylphosphono-2,3,7-trimethylpyrrolo-[1,2-*b*][1,2,4]triazine 5t

Yellow crystals, mp 94–95 °C [from dichloromethane–light petroleum (bp 40–60 °C)]; v_{max}(KBr)/cm^{-1} 1700 and 1015; δ_H 1.31–1.46 (9H, m, 2 OCH$_2$*Me* and CO$_2$CH$_2$*Me*), 2.52 (3H, s, Me), 2.57 (3H, s, Me), 2.68 (3H, s, Me), 4.11–4.29 (4H, m, 2 OC*H*$_2$Me) and 4.40 (2H, q, *J* 7, CO$_2$C*H*$_2$Me) (Found: C, 52.5; H, 6.45; N, 11.3%; M$^+$, 369.45. C$_{16}$H$_{24}$N$_3$O$_5$P requires C, 52.0; H, 6.55; N, 11.4%; *M*, 369.36).

6-Ethoxycarbonyl-5-diethylphosphono-7-methyl-1,2,3,4-tetra-hydrobenzo[*e*]pyrrolo[1,2-*b*][1,2,4]triazine 5u

Dark-orange oil; v_{max}(KBr)/cm^{-1} 1720 and 1020; δ_H 1.25–1.47 (9H, m, 2 OCH$_2$*Me* and CO$_2$CH$_2$*Me*), 1.92–1.99 (4H, m, cyclic CH$_2$), 2.69 (3H, s, Me), 2.92–3.02 (4H, m, 2 OC*H*$_2$Me) and 4.45 (2H, q, *J* 7, CO$_2$C*H*$_2$Me) (Found: C, 54.7; H, 6.7; N, 10.8%; M$^+$, 395.45. C$_{18}$H$_{26}$N$_3$O$_5$P requires C, 54.7; H, 6.6; N, 10.6%; *M*, 395.39).

6-Ethoxycarbonyl-5-diethylphosphono-7-methyl-2,3-diphenyl-pyrrolo[1,2-*b*][1,2,4]triazine 5v

Dark-yellow crystals, mp 119–120 °C (from diethyl ether); v_{max}(KBr)/cm^{-1} 1700 and 1020; δ_H 1.35 (6H, t, *J* 7, 2 OCH$_2$*Me*), 1.47 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 2.81 (3H, s, Me), 4.20–4.35 (4H, m, 2 OC*H*$_2$Me), 4.46 (2H, q, *J* 7, CO$_2$C*H*$_2$Me) and 7.28–7.47 (10H, m, 2 Ar) (Found: C, 63.2; H, 5.7; N, 8.6%; M$^+$, 493.65. C$_{26}$H$_{28}$N$_3$O$_5$P requires C, 63.3; H, 5.7; N, 8.5%; *M*, 493.49).

6-Ethoxycarbonyl-5-diethylphosphono-7-methyl-2-phenyl-pyrrolo[1,2-*b*][1,2,4]triazine 5w

Yellow crystals, mp 105–107 °C (from diethyl ether–pentane); v_{max}(KBr)/cm^{-1} 1710 and 1030; δ_H 1.37–1.49 (9H, m, 2 OCH$_2$*Me* and CO$_2$CH$_2$*Me*), 2.81 (3H, s, Me), 4.14–4.34 (4H, m, 2 OC*H*$_2$Me), 4.45 (2H, q, *J* 7, CO$_2$C*H*$_2$Me), 7.53–7.60 (3H, m, Ar), 8.00–8.04 (2H, m, Ar) and 8.76 (1H, s, CH); δ_C 10.36 (q), 14.80 (q), 16.94 (q), 17.08 (q), 61.99 (t), 62.80 (t), 62.88 (t), 96.35 (s), 122.37 (s, J_{CP} 8.7), 127.57 (d), 129.49 (s, J_{CP} 10.0),

130.00 (d), 131.64 (d), 133.49 (s), 136.58 (s, J_{CP} 17.0), 138.77 (d), 147.03 (s) and 165.08 (s) (Found: C, 57.6; H, 5.9; N, 10.1%; M⁺, 417.45. $C_{20}H_{24}N_3O_5P$ requires C, 57.55; H, 5.8; N, 10.1%; *M*, 417.40).

6-Ethoxycarbonyl-5-diethylphosphono-7-methyl-3-phenyl-pyrrolo[1,2-*b*][1,2,4]triazine 5x

Yellow oil; ν_{max}(KBr)/cm⁻¹ 1730 and 1040; δ_H 1.35–1.49 (9H, m, 2 OCH_2*Me* and CO$_2$CH$_2$*Me*), 2.77 (3H, s, Me), 4.20–4.34 (4H, m, 2 OCH_2Me), 4.45 (2H, q, *J* 7, CO$_2$CH_2Me), 7.51–7.56 (3H, m, Ar), 8.10–8.15 (2H, m, Ar) and 8.75 (1H, s, CH); δ_C 10.47 (q), 14.92 (q), 17.09 (q), 17.23 (q), 62.11 (t), 62.97 (t), 63.09 (t), 96.03 (s), 122.63 (s, J_{CP} 8.7), 127.66 (d), 129.36 (s, J_{CP} 10.0), 129.94 (d), 131.65 (s), 131.73 (d), 135.43 (s, J_{CP} 17.0), 137.30 (d), 145.82 (s) and 165.20 (s) (Found: C, 57.6; H, 5.8; N, 10.15%; M⁺, 417.45. $C_{20}H_{24}N_3O_5P$ requires C, 57.55; H, 5.8; N, 10.1%; *M*, 417.40).

Path C

The pyrrole derivative **1c** (1 mmol) and phenylglyoxal mono-hydrate (1 mmol) **2e** were dissolved in THF (5 cm³) and a cata-lytic amount of hydrochloric acid (35% w/w) was added to the solution. The reaction was complete in *ca.* 48 h, after which time evaporation of the reaction mixture under reduced pres-sure gave crude compound **4q**; this was recrystallised from diethyl ether and the pure product filtered off. The mother-liquor was purified on a silica gel column (cyclohexane–ethyl acetate mixtures) to yield **4r** and further **4q**. The imino deriv-atives **4q** and **4r** (1 mmol) were warmed in an oil-bath at 170 °C (*ca.* 0.5 h) and after work-up gave a dark residue which was purified by flash chromatography (cyclohexane–ethyl acetate) to afford compounds **5q** and **5r**.

Compound 4f

Yellow–orange powder, mp 213–215 °C [from diethyl ether–light petroleum (bp 40–60 °C)]; ν_{max}(KBr)/cm⁻¹ 3373, 1750, 1673, 1598, 1468, 1373 and 1341; δ_H([²H$_6$]-DMSO) 1.14 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.38 (9H, s, CO$_2$Bu'), 2.47 (3H, s, Me), 4.16 (2H, q, *J* 7, CO$_2$CH_2Me), 6.59 (1H, d, *J* 6.4, CH), 7.52–7.56 (3H, m, Ar), 7.68 (1H, d, *J* 6.4, OH, D$_2$O-exch.), 7.73 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$), 7.91–7.97 (2H, m, Ar) and 8.26 (2H, d, *J* 8.8, 4-NO$_2$C$_6$H$_4$); δ_C([²H$_6$]-DMSO) 10.85 (q), 13.94 (q), 27.37 (q), 59.54 (t), 73.43 (d), 84.87 (s), 107.94 (s), 114.90 (s), 122.38 (d), 126.39 (d), 129.11 (d), 129.25 (s), 131.36 (d), 131.53 (d), 134.42 (s), 135.40 (s), 140.17 (s), 145.59 (s), 152.47 (s), 157.41 (s) and 163.90 (s) (Found: C, 62.5; H, 5.2; N, 10.9. $C_{27}H_{28}N_4O_7$ requires C, 62.3; H, 5.4; N, 10.8%).

Compound 4k

Yellow powder, mp 131–135 °C (decomp.) [from diethyl ether–light petroleum (bp 40–60 °C)]; ν_{max}(KBr)/cm⁻¹ 3246, 2231, 1765, 1697, 1655 and 1603; δ_H([²H$_6$]-DMSO) 1.28–1.35 (12H, m, CO$_2$CH$_2$*Me* and CO$_2$Bu'), 2.42 (3H, s, Me), 4.30 (2H, q, *J* 7, CO$_2$CH_2Me), 7.52–7.77 (3H, m, Ar), 8.15 (2H, d, *J* 7.3, Ar), 8.85 (1H, s, CH) and 10.79 (1H, s, NH, D$_2$O-exch.); δ_C([²H$_6$]-DMSO) 10.42 (q), 13.97 (q), 27.57 (q), 60.52 (t), 81.60 (s), 114.35 (s), 126.36 (s), 127.98 (s), 128.50 (d), 130.15 (d), 133.78 (d), 134.51 (s), 139.82 (s), 141.58 (s), 154.00 (s), 156.94 (d), 164.11 (s) and 189.92 (s) (Found: C, 62.3; H, 5.9; N, 13.1. $C_{22}H_{24}N_4O_5$ requires C, 62.25; H, 5.7; N, 13.2%).

Compound 4q

Yellow–orange crystals, mp 162–166 °C (decomp.) [from diethyl ether–light petroleum (bp 40–60 °C)]; ν_{max}(KBr)/cm⁻¹ 3168, 1744, 1709, 1640, 1615 and 1593; δ_H([²H$_6$]-DMSO) 1.15–1.33 (18H, m, CO$_2$CH$_2$*Me*, CO$_2$Bu' and Pip), 2.41 (3H, s, Me), 3.07–3.96 (4H, m, Pip), 4.13–4.20 (2H, m, CO$_2$CH_2Me), 7.49–7.73 (3H, m, Ar), 8.11–8.17 (3H, m, CH and Ar) and 10.51 (1H, s, NH, D$_2$O-exch.); δ_C([²H$_6$]-DMSO) 10.48 (q), 14.12 (q), 23.93 (t), 24.80 (t), 25.84 (t), 27.60 (q), 41.55 (t), 46.89 (t),

59.77 (t), 81.02 (s), 108.05 (s), 110.94 (s), 128.30 (d), 130.15 (d), 130.61 (s), 133.21 (d), 134.94 (s), 139.70 (s), 150.65 (d), 154.26 (s), 162.83 (s), 163.09 (s) and 190.04 (s) (Found: C, 63.3; H, 6.9; N, 10.8. $C_{27}H_{34}N_4O_6$ requires C, 63.5; H, 6.7; N, 10.9%).

Compound 4r

Yellow powder, mp 159–161 °C (decomp.) (from diethyl ether); ν_{max}(KBr)/cm⁻¹ 3246, 1755, 1698, 1609 and 1577; δ_H([²H$_6$]-DMSO) 1.23 (3H, t, *J* 7, CO$_2$CH$_2$*Me*), 1.34 (11H, s, CO$_2$Bu' and Pip), 1.57 (4H, m, Pip), 2.42 (3H, s, Me), 3.13–3.26 (2H, m, Pip), 3.49–3.69 (2H, m, Pip), 4.16 (2H, q, *J* 7, CO$_2$CH_2Me), 6.52 (1H, d, *J* 6.4, CH), 7.53–7.55 (3H, m, Ar), 7.69 (1H, d, *J* 6.4, OH, D$_2$O-exch.) and 7.88–7.94 (2H, m, Ar); δ_C([²H$_6$]-DMSO) 10.41 (q), 14.20 (q), 24.19 (t), 25.32 (t), 25.75 (t), 27.40 (q), 41.87 (t), 47.41 (t), 59.49 (t), 73.70 (d), 84.79 (s), 107.42 (s), 112.80 (s), 126.26 (d), 127.30 (s), 129.15 (d), 131.32 (d), 134.55 (s), 152.66 (s), 156.65 (s), 162.86 (s) and 163.41 (s) (Found: C, 63.4; H, 6.8; N, 10.9. $C_{27}H_{34}N_4O_6$ requires C, 63.5; H, 6.7; N, 10.9%).

Compound 4x

Yellow powder, mp 154–155 °C (decomp.) (from diethyl ether); ν_{max}(KBr)/cm⁻¹ 3067, 1748, 1704 and 1560; δ_H([²H$_6$]-DMSO) 1.18–1.29 (9H, m, CO$_2$CH$_2$*Me* and 2 OCH$_2$*Me*), 1.35 (9H, s, CO$_2$Bu'), 2.36 (3H, s, Me), 3.90–4.04 (4H, m, 2 OCH_2Me), 4.22 (2H, q, *J* 7, CO$_2$CH_2Me), 6.54 (1H, q, *J* 6.4, CH), 7.58–7.61 (3H, m, Ar), 7.71 (1H, d, *J* 6.4, OH, D$_2$O-exch.) and 7.99–8.04 (2H, m, Ar); δ_C([²H$_6$]-DMSO) 10.33 (q), 14.03 (q), 16.11 (q), 16.25 (q), 27.37 (q), 59.89 (t), 61.19 (t, J_{CP} 2.9), 61.30 (t, J_{CP} 2.9), 72.88 (d), 85.04 (s), 98.78 (s), 112.50 (s, J_{CP} 8.7), 126.68 (d), 129.13 (d), 131.85 (d), 134.19 (s, J_{CP} 14.4), 134.56 (s), 134.57 (s, J_{CP} 23.1), 152.26 (s), 159.43 (s) and 163.53 (s) (Found: C, 56.3; H, 6.6; N, 7.7%. $C_{25}H_{34}N_3O_8P$ requires C, 56.1; H, 6.4; N, 7.85%).

Crystal structure of 6-ethoxycarbonyl-7-methyl-2-phenyl-5-piperidin-1-ylcarbonylpyrrolo[1,2-*b*][1,2,4]triazine 5r

Prismatic orange crystals suitable for X-ray analysis were pre-pared by recrystallisation from warm tetrahydrofuran.

Crystal data. $C_{22}H_{24}N_4O_3$, $M = 392.45$, triclinic, space group $P\bar{1}$, $a = 8.011(3)$, $b = 9.099(3)$, $c = 14.468(4)$ Å, $\alpha = 94.81(5)$, $\beta = 105.70(5)$, $\gamma = 86.99(4)°$, $U = 1011(1)$ Å³, $Z = 2$, $D_c = 1.29$ Mg m⁻³, $F(000) = 416$, $\lambda = 0.710\,69$ Å, $T = 298$ K, μ(Mo-Kα) = 0.088 mm⁻¹, crystal dimensions $0.80 \times 0.50 \times 0.15$ mm. A total of 3710 reflections were collected (3556 unique, $R_{int} = 0.0091$).

Data collection and processing. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Mo-Kα radiation, $\omega/2\theta$ scan mode, range $2.25° < \theta < 24.99°$. The unit-cell parameters were determined by least-squares refinement on diffractometer angles for 25 automatically centred reflections $7.4° < \theta < 12.8°$.

Structure analysis and refinement. The structure was solved by direct method and refined by full-matrix least-squares on F^2, using the SHELX program packages.[9,10] In the final refinement cycles 2659 reflections having $I > 2\sigma(I)$ were used, with 270 parameters varied. The weighting scheme used in the last refinement cycle was $w = 1/[\sigma^2(F_o^2) + (0.1076P)^2 + 0.3257P]$ where $P = (F_o^2 + 2F_c^2)/3$.

Since the ethyl ester group vibrates in a particular way, O(12), C(13) and C(14) were assigned as a rigid body having two posi-tions which on a refinement had occupancy factors of 0.78 and 0.22, respectively. Obviously, the temperature factors of these three atoms, plus the O(15) are much larger than the rest of the molecule. The hydrogen atoms were located by geometrical cal-culation and refined using a 'riding' model. The final agreement indices were $R_1 = 0.0595$ and $wR_2 = 0.1603$. Goodness of fit on $F^2 = 1.016$. Largest difference peak and hole was 0.346 and −0.506 e Å⁻³. Full crystallographic results for this X-ray determination have been deposited with the Cambridge

Crystallographic Data Centre.† Any request for this material should be accompanied by a full bibliographic citation for the paper together with the reference number CCDC 207/113.

---

† For details of the Scheme, see Instructions for Authors (1997), *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1.

Acknowledgements

References

1 J. G. Schantl, in *Houben-Weyl*, eds. H. Kropf and E. Schaumann, Thieme, Stuttgart, 4th edn., 1990, vol. E15, p. 909; J. G. Schantl, *Farmaco*, 1995, **50**, 379, and the references cited therein.
2 O. A. Attanasi and L. Caglioti, *Org. Prep. Proced. Int.*, 1986, **18**, 299, and the references cited therein.
3 G. Cirrincione, A. M. Almerico, E. Aiello and G. Dattolo, *Pyrroles Part 2: The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles*, ch. 3, *Aminopyrroles*, p. 299, ed. R. A. Jones, in the series *The Chemistry of Heterocyclic Compounds*, John Wiley & Sons, New York, 1992; G. P. Bean, *Pyrroles Part 1: The Synthesis and the Physical and Chemical Aspects of the Pyrrole Ring*, ch. 2, *The Synthesis of 1H-Pyrroles*, p. 107, ed. R. A. Jones, in the series *The Chemistry of Heterocyclic Compounds*, John Wiley & Sons, New York, 1990; A. Gossauer, *Die Chemie der Pyrrole*, Springer-Verlag, Berlin, 1974, and the references cited therein.
4 O. A. Attanasi, P. Filippone and F. Serra-Zanetti, in *Trends in Heterocyclic Chemistry*, ed. J. Menon, 1993, vol. 3, p. 461; O. A. Attanasi, P. Filippone and F. Serra-Zanetti, in *Progress in Heterocyclic Chemistry*, eds. H. Suschitzky and E. F. V. Scriven, Pergamon, Oxford, 1995, vol. 7, ch. 1, p. 1; O. A. Attanasi and P. Filippone, in *Topics in Heterocyclic Systems–Synthesis, Reactions and Properties*, eds. O. A. Attanasi and D. Spinelli, 1996, vol. 1, p. 157.
5 O. A. Attanasi and P. Filippone, *Synlett*, in press, and the references cited therein.
6 F. W. McOmie, *Protective Groups in Organic Chemistry*, Plenum, London, 1973; T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, 1991; P. J. Kocienski, *Protecting Groups*, George Thieme Verlag, Stuttgart, 1994.
7 J. G. Erickson, *Chem. Heterocycl. Compd.*, 1956, **10**, 44; R. L. Jones and J. R. Kershaw, *Rev. Pure Appl. Chem.*, 1971, **21**, 23; H. Neunhoeffer and P. F. Wiley, *Chem. Heterocycl. Compd.*, 1978, **33**, 189; J. P. Horwitz, in *Heterocyclic Compounds*, ed. R. C. Elderfield, John Wiley & Sons, Inc., New York, 1961, vol. 7, p. 1; H. Neunhoeffer, *1,2,4 Triazines and Benzo Derivatives*, ed. A. J. Boulton, vol. 6, ch. 14, in the series *Comprehensive Heterocyclic Chemistry II*, eds. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon-Elsevier Science, Amsterdam, 1996; E. S. H. El Ashry, N. Rashed, M. Taha and E. Ramadan, *Adv. Heterocycl. Chem.*, 1994, **59**, 39.
8 O. A. Attanasi, S. Santeusanio, F. Serra-Zanetti, E. Foresti and A. McKillop, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1669; O. A. Attanasi, L. De Crescentini, S. Santeusanio, F. Serra-Zanetti, A. McKillop and Z. Liao, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1009; O. A. Attanasi, Z. Liao, A. McKillop, S. Santeusanio and F. Serra-Zanetti, *J. Chem. Soc., Perkin Trans. 1*, 1993, 315; O. A. Attanasi, P. Filippone, D. Giovagnoli and A. Mei, *Synthesis*, 1994, 181.
9 G. M. Sheldrick, SHELXS-86, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
10 G. M. Sheldrick, SHELXL-93, a computer program for crystal structure determination, University of Göttingen, Germany, 1993.